REMARKS

The Invention

The invention is drawn to methods for detecting cancer of an organ in a specimen of a body fluid that drains the organ. The specimen can be blood, urine, sputum, bile, stool, cervical smears, saliva, tears, cerebral spinal fluid, or lymph nodes. A plurality of microsatellite markers in the specimen is tested to determine a microsatellite marker length alteration in the specimen relative to a control sample. A microsatellite marker length alteration in the specimen relative to the control sample indicates the presence of a cancer in the organ that drains into the body fluid. (Claim 24.) The method may be used to detect lung cancer in a sputum specimen (claim 23), or to detect bladder cancer in a urine specimen (claim 31).

The invention is also drawn to a method for detecting cancer cells in a histopathological margin specimen external to a primary tumor. A plurality of microsatellite markers in a histopathological margin specimen external to a primary tumor is tested to determine a microsatellite marker length alteration relative to a control sample. A length alteration indicates the presence of cancer cells in the specimen. (Claim 34.)

Amendments

The preamble of claim 34 has been amended to recite a method for detecting cancer cells in a --histopathological margin-- specimen. The amendment is supported by the body of the claim which recites "testing a plurality of microsatellite markers in a histopathological margin

specimen." (Line 3.) Thus the amendment neither narrows the claim nor introduces new matter.

New claims 38-45 have been added. Claims 38-45 are dependent on claim 24. Each of the newly added claims individually recites one specimen that is recited in the Markush group of specimens disclosed in independent claim 24. Thus the newly added claims also introduce no new matter.

The Rejection of Claims 24-28, and 37 Under Double Patenting

Claims 24-28, and 37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,235,470. Upon indication of allowability of claims 24-28 and 37 applicants will file a terminal disclaimer. Abeyance of this rejection is respectfully requested.

The Rejection of Claims 24-28, and 37 Under 35 U.S.C. § 103 (a)

Claims 24-28, and 37 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Brugieres et al. (Cancer Research, Feb. 1993, vol. 53, pp 452-455) in view of Gonzalez-Zulueta (Cancer Research 1993), Merlo et al., (Cancer Research 1994), and Ah-See et al. (Cancer Research, 1994). Applicants respectfully traverse.

A *prima facie* case of obviousness of a claim under 35 U.S.C. §103(a) requires that the references teach or suggest all limitations of the claim. It is respectfully submitted that the combination of Burgieres et al., Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. do not teach all the limitations of claim 24. Claim 24 recites:

> A method for detecting cancer of an organ in ***a specimen of a body fluid which drains the organ***, wherein the specimen is

> selected from the group consisting of: blood, urine, sputum, bile, stool, cervical smears, saliva, tears, cerebral spinal fluid, and lymph nodes, comprising the step of:
>
> testing a plurality of microsatellite markers in ***the specimen*** to determine a microsatellite marker length alteration relative to a control sample, wherein a microsatellite marker length alteration in the specimen relative to the control sample indicates the ***presence of a cancer in the organ which drains into the body fluid***.

Emphasis added. The claimed method is drawn to detecting cancer of an organ by testing a body fluid that drains the organ. None of the references, Burgieres et al., Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. teach this limitation of claim 24.

Burgieres et al. teach "the results of screening for p53 germ line mutations on a first set of ten families, eight of them identified through a proband with sarcoma." (Emphasis added, page 452, second column, lines 7-9.) Burgieres et al. tested whole blood samples. Thus Burgieres et al. teach the identification of p53 mutations that are found in all cells of an individual; the mutation is a germ line mutation. Burgieres et al. does not teach testing a body fluid that drains an organ. Burgieres et al. does not teach that a p53 mutation indicates the presence of cancer in an organ as required in claim 24. Thus Burgieres et al. does not teach this limitation of claim 24.

Gonzalez-Zulueta et al. also do not teach this limitation of claim 24. Gonzalez-Zulueta et al. teach "that genomic instability as measured by changes in microsatellite repeats occurs in TCC of the bladder." (Emphasis added, page 5622, first column, lines 1-2 of the Discussion.) Gonzalez-Zulueta et al. teach determining microsatellite repeat polymorphisms in the bladder cancer cells. Thus Gonzalez-Zulueta et al. does not teach determining microsatellite repeat polymorphisms in a body fluid that drains an organ.

Merlo et al. also do not teach identification of a cancer by determining microsatellite repeat polymorphisms in a body fluid that drains an organ. Merlo et al. teach "many small cell lung cancers display widespread microsatellite alteration potentially constituting a distinct RER phenotype." (Emphasis added, page 2098, second column, lines 9-11.) Thus Merlo et al. teach determining microsatellite alteration in the tumor sample, not a body fluid that drains an organ.

Ah-See et al. also do not teach identification of a cancer by determining microsatellite repeat polymorphisms in a body fluid that drains an organ. Ah-See et al. teach comparing "normal and tumor DNA from 28 patients using a battery of 50 markers." (Emphasis added, page 1617, second column, lines 4-5.) Thus, Ah-See et al. teach detection of microsatellite repeat polymorphisms in the cells of the tumor, and not in a body fluid that drains an organ.

The combination of Burgieres et al., Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. fails to teach all the limitations of claim 24. None of the references teaches detecting cancer of an organ in a specimen of a body fluid which drains the organ. Thus the PTO fails to present a *prima facie* case of obviousness. Withdrawal of this rejection of claim 24, and dependent claims 25-28, and 37 is respectfully requested.

The Rejection of 34 Under 35 U.S.C. § 103 (a)

Claim 34 is rejected under 35 U.S.C. § 103 (a) as being unpatentable over Hayashi et al. (Cancer Research, July 1994, Vol. 54, p 3853-3856), in view of Gonzalez-Zulueta (Cancer Research 1993), Merlo et al. (Cancer Research 1994), and Ah-See et al. (Cancer Research, 1994). Applicants respectfully traverse.

Amended claim 34 requires that the tested specimen be a histopathological margin specimen which is external to the primary tumor. None of the cited references teach this element of the claim. None of Hayashi et al., Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. teach the determination of microsatellite length in a histopathological margin specimen external to a primary tumor.

Hayashi et al. teach screening of "22 colorectal cancers for K-ras and p53 mutations and examined corresponding regional lymph node at the genetic level by the MASA [mutant allele-specific amplification] method." (Page 3853, first column, lines 4-6 of the Abstract.) Thus, Hayashi et al. teach the determination of K-ras and p53 mutations in lymph nodes, which are distinct organs from the tumor. Hayashi et al. do not teach examination of a genetic alteration in a histopathological margin specimen, which is immediately adjacent to a tumor in the same organ.

The Office Action asserts that "from the teaching of Hayashi, the ordinary artisan would have been taught that cancer cells can be found in regions external to primary tumors and that such cancer cells are not necessarily detectable by traditional histopathological methods." (Paper 19, page 5, last 3 lines.) However, Hayashi et al., as a whole, teaches detection of tumors that have metastasized to lymph nodes. Hayashi et al. teach examination of lymph node DNA for mutations to determine if a cancer has spread to a secondary site. The method of claim 34 is not drawn to detection of metastasis, *i.e.*, cancer that has spread to secondary sites in the patient. The specification discloses that the histopathological margin specimen is a specimen that surrounds the tumor.

> The method can also be used to detect a hypermutable nucleic acid sequence associated with a primary tumor by assaying the

> surrounding tumor margin. As used herein the term "tumor margin" refers to the tissue surrounding a discernible tumor. In the case of surgical removal of a solid tumor, the tumor margin is the tissue cut away with the discernible tumor that usually appears to be normal to the naked eye. More particularly, as used herein, "margin" refers to the edge, border, or boundary of a tumor. The margin generally extends from about 0.2 cm to about 3 cm from the primary tumor but can be greater depending upon the size of the primary solid tumor.

Emphasis added, page 9, lines 10-18. Thus, the method of claim 34 is directed to testing tissue of the organ surrounding the tumor. In contrast, the method taught by Hayashi, as a whole, is directed to testing metastases to another organ. There is no suggestion in the art to modify the teachings of Hayashi et al. In fact, modification of Hayashi et al. to detect a genetic alteration in the tissue surrounding a tumor would so alter Hayashi et al. that it would no longer teach "genetic diagnosis of occult metastases." (Page 3853, second column, lines 8-9.)

Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. do not teach detection of microsatellite marker length alterations in a histopathological margin specimen of a tumor. Thus Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. do not remedy the defect of Hayashi et al. As indicated previously, Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. each teach detection of microsatellite instability in the cells of the tumor. Thus the combination of Hayashi et al., Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. do not teach or suggest the detection of microsatellite marker length alterations in a histopathological margin specimen of a tumor. The *prima facie* case is defective because none of the references teach this element of the claim. Withdrawal of this rejection of claim 34 is respectfully requested.

Respectfully submitted,

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Appendix 1: Marked up version to show changes made

34. (Amended) A method for detecting cancer cells in a histopathological margin specimen external to a primary tumor comprising the steps of:

testing a plurality of microsatellite markers in a histopathological margin specimen external to a primary tumor to determine a microsatellite marker length alteration relative to a control sample, wherein a length alteration indicates the presence of cancer cells in the specimen.